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Original Article

Dose Escalation by Intensity-modulated Radiotherapy Boost after Whole Pelvic Radiotherapy in Postoperative Patients of Carcinoma Cervix with Residual Disease

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Abstract

Aims: External beam radiotherapy followed by brachytherapy is the standard treatment for patients with carcinoma cervix. However, for patients who come from peripheral hospitals after incomplete surgery, whole pelvic radiotherapy (WPRT) followed by boost with either vaginal vault brachytherapy if suitable or further external beam radiotherapy is recommended. This study was conducted to evaluate if it was possible to give a higher tumour dose using intensity-modulated radiotherapy for that group of patients who were not suitable for high dose rate vaginal vault brachytherapy because of gross disease after WPRT.
Materials and methods: A prospective study was carried out from 2005 to 2010 in which 25 postoperative patients of cervical carcinoma with gross residual disease after WPRT of 46 Gy/23 fractions/4.5 weeks were included. Nine patients were treated with 20 Gy to the planning target volume and 30 Gy to the clinical target volume in 10 fractions; 16 patients were treated with 30 Gy to the planning target volume and 35 Gy to the clinical target volume in 15 fractions. The end points of this study were local control, survival and treatment-related toxicity.
Results: The median follow-up was 38 months. The 3 year local control, progression-free survival and overall survival rates were 76, 74 and 67%, respectively. Late grade 2 rectal toxicity was seen in 11 patients. Grade 2 bladder toxicity occurred in two patients and grade 3 bowel toxicity in two patients. No other grade 3 or higher toxicity was seen.
Conclusion: Inadequate and inappropriate surgery in invasive cervical cancer with resulting gross residual disease is common in India. It is possible to escalate the tumour dose by intensity-modulated radiotherapy boost after WPRT in postoperative cervical carcinoma patients with gross residual disease with low incidence of severe toxicity and excellent local control.

Key words: Cervical carcinoma; inadequate surgery; intensity-modulated radiotherapy; postoperative; toxicity; vaginal vault brachytherapy

Introduction

Cervical cancer is the most common malignancy affecting women in India [1]. Radical hysterectomy or radical radiotherapy alone is traditionally the first choice of treatment for early invasive cervical cancer. However, most of our patients present with locally advanced disease where radical surgery is not possible. Despite this, many of these undergo incomplete surgery at peripheral hospitals owing to a lack of proper investigative evaluations and/or a lack of expertise. Whole pelvic radiotherapy (WPRT) followed by a boost to the tumour site is the standard of practice for the radiotherapeutic management of patients with gross residual disease after incomplete surgery. Traditionally, doses in excess of 75–85 Gy have been prescribed to point A for curative treatment of carcinoma cervix [2]. However, in postoperative patients with gross residual local disease after WPRT, the outcome is dismal, as these are not suitable for vaginal brachytherapy and doses in excess of 60–66 Gy cannot be delivered safely with external beam radiotherapy alone due to the increase in rectal and bladder complications. In a retrospective analysis published from our institute by Saibishkumar *et al.* [3], patients with gross residual disease had a disease-free survival rate of 40.9%, an overall survival rate of 45.5% and a pelvic control rate of 68.2%. On subgroup analysis, it was found that 19 patients with gross residual disease not suitable for brachytherapy after WPRT (46 Gy/23 fractions/4.5 weeks), when treated with supplementary radiotherapy (20 Gy in 10 fractions) had much inferior disease-free survival (10.5%), overall survival

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(15.8%) and pelvic control rates (47.4%). Before the start of the present study, patients with gross local residual disease without pelvic or para-aortic lymphadenopathy after WPRT were treated with supplementary radiotherapy of 20 Gy in 10 fractions in 2 weeks. In an attempt to improve local control and outcome in this subgroup of patients, a dose escalation study using an intensity-modulated radiotherapy (IMRT) boost schedule to deliver a higher dose to the tumour-bearing area was designed. The higher conformality of the IMRT dose distribution allows significant sparing of the organs at risk. To the best of our knowledge, this is the only study of its kind.

Materials and Methods

Patients

Between 2005 and 2010, 252 patients were evaluable out of 278 registered in our department after undergoing incomplete surgery elsewhere. Of 252, 198 patients were treated with WPRT followed by vault brachytherapy, 29 patients were treated with supplementary radiotherapy because of pelvic or para-aortic node involvement. The remaining 25 patients with gross residual disease were included in this prospective study. All patients had a pretreatment work-up including cystoscopy and computed tomography of the abdomen and pelvis. The demographic profile of patients is given in Table 1. All patients were treated with standard WPRT using a four-field box technique on a 6 or 15 MV linear accelerator delivering a dose of 46 Gy in 23 fractions in 4.5 weeks. Sixteen patients received concomitant chemotherapy with weekly cisplatin. At the end of external beam radiotherapy, patients were assessed for high dose rate vaginal vault brachytherapy. Patients were considered eligible for the study if they had gross residual local disease after standard WPRT and were not suitable for vaginal vault brachytherapy. Gross residual local disease was defined as disease more than 1 cm thickness at or beyond the vaginal vault that cannot be covered by vaginal vault ovoid brachytherapy alone. Patients were excluded if they had pelvic or para-aortic lymphadenopathy, distant metastasis, Karnofsky performance status less than 70 and any uncontrolled comorbid conditions. All patients signed a written informed consent before participation in the study. Ethical clearance for the conduction of the study was obtained from the institutional ethics committee before the inception of the study.

Table 1
Demographic profile

Age (years)	
Range	30–60
Median	47
Size of residual disease	
≤4 cm	14 (56%)
>4 cm	11 (44%)
Parametrial involvement	
Free	1 (4%)
Short of lateral pelvic wall	6 (24%)
Up to lateral pelvic wall	18 (72%)
Histological type	
Squamous	23 (92%)
Adenocarcinomas	1 (4%)
Adenosquamous	1 (4%)

Intensity-modulated Radiotherapy Treatment Planning and Delivery

After the completion of WPRT, all patients underwent planning computed tomography with 2.5 mm slices in the Light Speed VFX-16 CT simulator. Patients were immobilised and positioned with aids such as vacuum bags and knee wedges. Planning was carried out on Eclipse treatment planning Varian Medical system version 8.6. The clinical target volume (CTV) delineation consisted of all clinically and radiologically demonstrable residual tumour, vault, parametrium and upper half to two-thirds of vagina depending on vaginal extension. The pelvic and para-aortic nodal volumes were not included in the target volume. This target volume was expanded by 1 cm in the lateral, craniocaudal and anterioposterior directions to create the planning target volume (PTV; as per institutional protocol). The organs at risk contoured were the bowel, rectum and bladder. The rectum was contoured from the anus to the rectosigmoid flexure as a solid organ. The bladder was also contoured as a solid organ. In order to account for the displacements in bowel loops, the entire peritoneal cavity was contoured up to 2 cm above the superior-most extent of the PTV. Patients were simulated and treated 15 min after bladder emptying so that some amount of residual urine remains and in order to decrease the volume of bladder and bowel in the fields.

IMRT planning was carried out using seven photon beams (6 MV) coplanar at intervals of 51°. Plan optimisation was carried out by inverse planning technique using Helios IMRT software with the help of the dose volume optimisation algorithm, version 8.6.

This was a prospective non-randomised study carried out to assess the feasibility of IMRT boost to vault without increasing normal tissue toxicity. The objective of this study was to give a higher dose to the tumour-bearing area while respecting the tolerance of normal tissues. Two dose schedules were used. At the start of the protocol, nine patients were treated with a dose of 20 Gy in 10 fractions over 2 weeks to the PTV. The CTV was prescribed a dose of 30 Gy simultaneously. Thus, the CTV received a total dose of 76 Gy. All these patients had acceptable toxicity, but three had local failure. Therefore, the dose was further escalated and the subsequent patients were treated with a dose of 30 Gy to the PTV in 15 fractions with a simultaneous boost to the CTV to a dose of 35 Gy. The total dose in this cohort was 81 Gy. The biologically effective dose (BED) and the equivalent dose in 2 Gy (EQD_2) to the tumour (CTV) using the linear-quadratic model (a/b = 10 Gy) were calculated using the formulas: